

following remarks are courteously requested.

By the foregoing amendment, claims 1 and 4 have been amended. No claims are added or canceled. Thus, claims 1 to 6 are currently pending for the Examiner's consideration.

In the Office Action, the Examiner rejected claims 1 to 6 under 35 U.S.C. § 112, second paragraph as being indefinite. The claims have been reviewed, and the present amendment is believed to overcome the rejections. It is also noted that in answer to the Examiner's question, claim 4 is not necessarily directed to the use of a plurality of labels, but rather to a plurality of peaks for mutational inspected sites.

The Examiner rejected claims 1 and 3 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,795,976 ("Oefner"). The Examiner further rejected claims 2, and 4 to 6 under 35 U.S.C. § 103(a) as being unpatentable over Oefner in view of U.S. Patent No. 6,265,557 ("Diamond"). These rejections are respectfully traversed.

The present invention is directed to a method of detecting mutations in the base sequence of a nucleic acid where the method enables discrimination and inspection of mutations in the base sequence of **a plurality of inspected cites** in a **single** nucleic acid, and in a **single** analysis.

Oefner discloses a method for detecting a nucleic acid heteroduplex molecule. Oefner uses oligonucleotides to hybridize a nucleic acid fragment. The Examiner cites column

4, lines 16 to 43 of Oefner for this teaching. However, this passage in Oefner is not directed to the use of "*a plurality of types of oligonucleotides that are labeled to be discriminable from each other*" as claimed in claim 1. The reason for this is that Oefner's method is only suitable for the detection of single base-pair mismatches in a nucleic acid, or consecutive base-pair mismatches that are flanked by matching base pairs. In other words, the Oefner method is similar to those disclosed in the background section of the present application, and suffers from the same inadequacies, namely, the inability to detect and adequately analyze a plurality of sites that may have base pair mismatches.

From the above discussion, it is clear that Oefner also fails to teach or suggest the feature in claim 1 where "*a plurality of inspected sites to be subjected to inspection of mutation in the base sequence [are hybridized] with a plurality of types of oligonucleotides...*" Oefner repeatedly teaches that the method disclosed therein is suitable for detecting a single base pair mismatch in a nucleic acid of up to 2,000 bp, but fails to teach or suggest the detection of a plurality of mismatches, which would require a plurality of oligonucleotides. For at least the above reasons, the rejections of claims 1 and 3 based solely on the Oefner reference should be overcome.

As mentioned above, Diamond is only cited for its teachings of the use of fluorescent labeling of oligonucleotide primers and probes to distinguish one from another. The primers and probes are specific to individual alleles in a genome. Nevertheless, Diamond fails to compensate the failure of Oefner to teach or suggest the feature in claim 1 of *"hybridizing ... a plurality of inspected cites to be subjected to inspected of mutation in the base sequence with a plurality of types of oligonucleotides...."* Although Diamond discloses the use of two separate oligonucleotides (col. 22, lines 7 to 11, for example), the separate nucleotides are directed to single inspection cites, such as the ABO locus, where variance in the inspection cite lies in the differences between several alleles for blood type. Consequently, Diamond fails to compensate for the deficient teachings of Oefner discussed above.

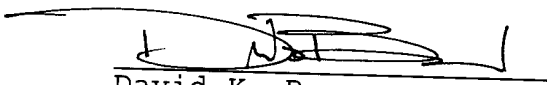
"A claim is anticipated [under 35 U.S.C. § 102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) (emphasis added). See M.P.E.P. § 2131. Likewise, "to establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In *re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)." M.P.E.P. §

2143.03. Accord. M.P.E.P. § 706.02(j). Because the features discussed above in the claims are neither taught nor suggested by the combination of Oefner and Diamond, it is respectfully requested that the rejections of claims to 6 be withdrawn.

For the foregoing reasons, all the claims now pending in the present application are believed to be clearly patentable over the prior art of record. Accordingly, favorable reconsideration of the claims in light of the above remarks is courteously solicited. If the Examiner has any comments or suggestions that could place this application in even better form, the Examiner is requested to telephone the undersigned attorney at the below-listed number.

Respectfully submitted,

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Appendix

Amendments to the Claims

1. (amended) A method of detecting mutation in the base sequence of nucleic acid, including:

(A) a bonding step of hybridizing an object of analysis, consisting of nucleic acid or a nucleic acid fragment including a plurality of inspected sites to be subjected to inspection of mutation in the base sequence, with a plurality of [types of] labeled oligonucleotides of varying types, each oligonucleotide having a base sequence that is complementary to [any] at least one normal base sequence of one of the inspected sites [having normal base sequence], and each oligonucleotide being labeled to be discriminable from each other for forming duplexes including hetero- and homoduplexes; and

(B) a detection step of employing an ion pair chromatograph comprising a reversed phase column serving as a separation column and a detector capable of discriminating and detecting the labeled oligonucleotides, and setting the separation column at a temperature [causing the] at which there is a difference in stability between the hetero- and homoduplexes included in the duplexes for analyzing the object of analysis.

4. (amended) The mutation detecting method according to claim 1, which further comprises observing a chromatogram of labels obtained through the detection step (B), and thereby [for] determining that an inspected site corresponding to a label is non-mutational due to the presence of [having] a single peak [as non-mutational], while further determining that an inspected site corresponding to a label is mutational due to the presence of [having] two peaks [as mutational].